American Journal of Hematology 63:32–34 (2000)

# Haemorrhagic Cystitis Associated With Adenovirus in a Patient With AIDS Treated for a Non-Hodgkin's Lymphoma

**David Ghez,[1] Eric Oksenhendler,[1] Catherine Scieux,[2] and Kaïss Lassoued[1]***

[1]Service d'Immuno-Hématologie, Hôpital Saint-Louis, Paris, France
[2]Laboratoire de Virologie, Hôpital Saint-Louis, Paris, France

**Adenovirus-induced haemorrhagic cystitis has been reported chiefly in bone marrow or kidney transplant recipients. We report hereon an HIV-positive patient treated for a Burkitt's lymphoma who developed gross haematuria associated with fever and burning urination. Usual causes of haematuria were ruled out: lithiasis, urinary tract lesions, glomerulonephritis, mycobacterium and schistosoma infections, and drug toxicity. Adenovirus was detected by cellular cultures and BK/JC virus DNA sequences were detected using a polymerase chain reaction method. Because BK/JC virus shedding is very common (75%) in HIV patients receiving chemotherapy, our data strongly suggest that adenovirus was responsible for the haemorrhagic cystitis in our patient. In conclusion, adenovirus should be considered as a potential cause of haemorrhagic cystitis in AIDS patients whose immunosuppression is aggravated by cytotoxic drugs. Am. J. Hematol. 63:32–34, 2000.** 

**Key words: adenovirus; BK virus; JC virus; haemorrhagic cystitis; HIV**

## INTRODUCTION

Adenoviruses have been held responsible for haemorrhagic cystitis after bone marrow and kidney transplantation [1,2] but never in patients with AIDS. We report the case of a patient infected with the HIV and treated for a non-Hodgkin's lymphoma who developed a severe haemorrhagic cystitis associated with an adenovirus infection.

## MATERIALS AND METHODS

Urine specimens in viral transport medium were inoculated onto human fibroblast cells (MRC5) for both rapid and conventional culture technique. The rapid 48-h culture technique was performed by using 96-well plate centrifugation and immunoperoxydase staining with adenovirus monoclonal antibody (H-60 clone, Argene, France) as previously reported [3]. Conventional cell culture plates were observed periodically for cytopathic effects. Typing of adenovirus subgenus isolates was determined by polymerase chain reaction (PCR) as previously described [4].

Detection of BK virus DNA in urine specimens was performed by PCR as previously described [5].

## CASE REPORT

A 34-year old HIV-positive Caribbean patient was referred for a Burkitt's lymphoma. He presented with an hepatosplenomegaly, generalized lymphadenopathies, fever, and weight loss. A bone marrow aspirate showed Burkitt's cells and the karyotype a t(8;14) translocation. CD4+ T lymphocyte count was $289 \times 10^6$/l, and the HIV viral load was about 72,000 copies/ml. The treatment consisted in combination chemotherapy cycles according to the LMB 86 regimen [6]. He was in complete remission after 3 cycles which included cyclophosphamide, vincristine, adriblastin, and methotrexate. During each

*Correspondence to: Dr. K. Lassoued, Service d'Immuno-Hématologie, Hôpital Saint-Louis, 1, Avenue Claude Vellefaux, 75475 Paris Cedex 10, France. E-mail: kaiss.lassoued@sa.u-picardie.fr

Received for publication 1 June 1999; Accepted 1 September 1999

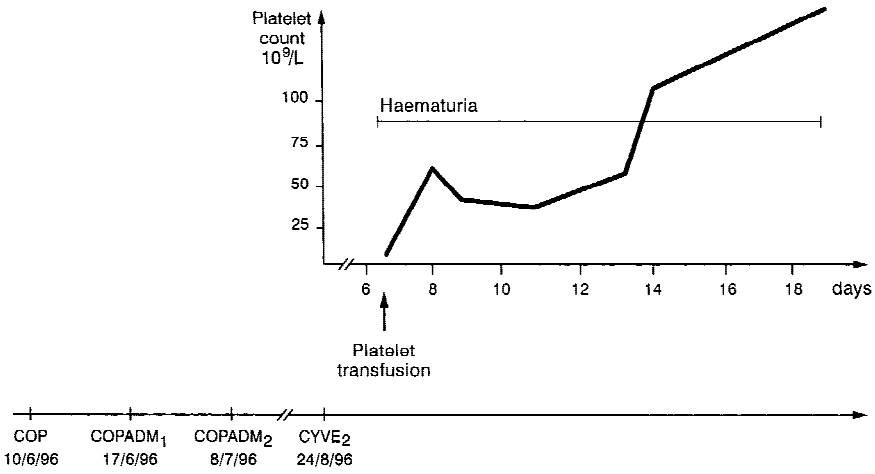


**Fig. 1. Sequential platelet counts during the haematuric period.**

cycle comprising cyclophosphamide, he received infusions of 2-mercaptosulfoethane (mesna) for uroepithelium protection. He then received two cycles of the CYVE regimen, which consists in cytarabine and etoposide over a 4-day period (Fig. 1).

Sixteen days after the final injection of the second CYVE cycle, he developed gross haematuria associated with frequent burning urination and fever. His blood cell count showed $0.1 \times 10^9$/l WBC, $7 \times 10^9$/l platelets, and haemoglobin was 9 g/dl. The haematuria persisted following a platelet transfusion that raised the platelet count to $58 \times 10^9$/l. There was no other sign of haemorrhage, and the haemostasis was normal. The haematuria persisted for over 10 days, although the platelet count increased spontaneously to over $100 \times 10^9$/l (Fig. 1). The fever persisted although the neutropenia had disappeared and the patient was given antibiotic therapy.

Standard and mycobacterium urine cultures were sterile, and schistosoma eggs were undetected. Adenovirus (subgroup A, type 12, 18, or 31) was detected by cellular culture, and BK/JC viruses common DNA sequences were found using a polymerase chain reaction method.

The patient was not receiving any antiretroviral treatment in particular no antiproteases which are known to cause nephrolithiasis. A urinary tract ultrasound was considered to be normal. There was evidence of neither kidney nor ureteral lithiasis on abdominal X-rays. A cystoscopy could not be performed because the patient refused it. In addition, there was no evidence of a glomerulonephritis which could have explained the haematuria and renal function remained normal.

The haematuria spontaneously resolved within 10 days, and chemotherapy was pursued. Further urine analysis did not show any proteinuria or microscopic haematuria. The patient is still in complete remission and has not experienced another episode of haemorrhagic cystitis.

## DISCUSSION

In the case discussed herein, there is a great body of evidence which suggests that the adenovirus is the cause of the haemorrhagic cystitis. No other infectious cause was found, neither lithiasis nor any other urinary tract lesion. There was no evidence of a glomerulonephritis. The platelet count was low at the onset of the haemorrhagic cystitis however there was no other sign of haemorrhage and the haematuria persisted for nearly 10 days after the platelet count had been over $100 \times 10^9$/l. In addition, the fever persisted despite antibiotherapy. The fever and the haemorrhage subsided simultaneously. It is doubtful that cyclophosphamide was responsible for the haematuria as the last injection had been administered 2 months prior; furthermore, saline hydration and mesna had been used preventatively. BK or JC viruses might have been incriminated as they are both known to cause haemorrhagic cystitis in immunodeficient hosts, and BK/JC DNA common sequences had been detected by PCR in our patients. However, the incidence of asymptomatic BK/JC viruria appears to be relatively high in both immunocompetent and HIV-positive patients. Markowitz et al. showed that urine shedding of these viruses in HIV-infected patients is 20.6% for BKV and 24% for JCV [7]. In our own experience, 9 out of 12 patients (75%) with AIDS treated by chemotherapy for non-Hodgkin's lymphomas had a positive PCR for BK/JC viruses in their urine whereas only one shed adenovirus (patient reported herein). Therefore it seems difficult to associate accurately haemorrhagic cystitis and BK/JC viruria, although a causal role played by BK/JC virus cannot be ruled out in this case.

Haemorrhagic cystitis associated with adenovirus (usually type 11) is a rare event described chiefly in bone marrow [1,8] or kidney transplant recipients [2]. Haemorrhagic cystitis usually occurs between 15 and 60 days following bone marrow transplantation [8]. In kidney transplantation, the risk is maximal within the first 3

months and persists for a year. The onset of the cystitis thus suggests that it is related to the maximal immunosuppression. The cystitis is usually self-limiting, but it can be severe and require multiple blood transfusion. In such cases, intravenous ribavirin therapy has appeared effective [9].

Although there has been a case of asymptomatic necrotizing infection of the renal tubules due to an adenovirus in a patient infected with the HIV [10], adenovirus-related haemorrhagic cystitis has never been reported in AIDS. Immunosuppression caused by the HIV infection and aggravated by chemotherapy seems to be necessary for the development of a symptomatic uroepithelial infection. It is our belief that adenovirus should be considered as another potential cause of haemorrhagic cystitis in patients with AIDS treated with cytotoxic drugs.

## ACKNOWLEDGMENTS

We thank Prof. Freymuth, from the Virology Laboratory of the Hôpital de Caen, who determined the subgroup of the adenovirus.

## REFERENCES

1. Ambinder RF, Burns W, Charache P, Arthur R, Beschorner W, Santos G, Saral R. Hemorrhagic cystitis associated with adenovirus infection in bone marrow transplantation. Arch Intern Med 1986;146:1400–1401.
2. Koga S, Shindo K, Matsuya F, Hori T, Kanda S, Kanetake H. Acute hemorrhagic cystitis caused by adenovirus following renal transplantation: review of the literature. J Urol 1993;149:838–839.
3. Trabelsi A, Pozzetto B, Mbida AD, Grattard F, Ros A, Gaudin OG. Evaluation of four methods for rapid detection of adenovirus. Eur J Clin Microbiol Infect Dis 1992;11:535–539.
4. Kidd AH, Jonsson M, Garwicz D, Kajon AE, Wermenbol AG, Verweij MW, de Jong JC. Rapid subgenus identification of human adenovirus isolates by a general PCR. J Clin Microbiol 1996;34:622–627.
5. Arthur R, Dagostin S, Shah K. Detection of BK virus and JC virus in urine and brain tissue by the polymerase chain reaction. J Clin Microbiol 1989;27:1174–1179.
6. Soussain C, Patte C, Ostronoff M, Delmer A, Rigal-Huguet F, Cambier N, Lepris PY, Francois S, Cony-Makhoul P, Harousseau JL. Small noncleaved cell lymphoma and leukemia in adults. A retrospective study of 65 adults treated with the LMB pediatric protocols. Blood 1995;85:664–674.
7. Markowitz RB, Thompson HC, Mueller JI, Cohen JA, Dynan WS. Incidence of BK virus and JC virus viruria in human immunodeficiency virus-infected and -uninfected subjects. J Infect Dis 1993;167:13–20.
8. Miyamura K, Takeyama K, Kojima S, Minami S, Matsuyama K, Morishima Y, Kodera Y. Hemorrhagic cystitis associated with urinary excretion of adenovirus type 11 following allogeneic bone marrow transplantation. Bone Marrow Transplant 1989;4:533–535.
9. Murphy GF, Wood DP, Jr, McRoberts JW, Henslee-Downey PJ. Adenovirus-associated hemorrhagic cystitis treated with intravenous ribavirin. J Urol 1993;149:565–566.
10. Green WR, Greaves WL, Frederick WR, Tadesse-Health L. Renal infection due to adenovirus in a patient with HIV infection. Clin Infect Dis 1994;18:989–991.